

Original Article

Multiple paraneoplastic syndromes associated with small cell lung cancer: a unique case of concomitant Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration and syndrome of inappropriate secretion of antidiuretic hormone

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Abstract: Paraneoplastic syndromes (PNS) is not caused by direct invasion of tumor or its metastasis, but presumably immune mediated remote effects of cancer on other systems or organs. Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disease of the neuromuscular junction, and about half of the patients with LEMS have a tumor. Paraneoplastic cerebellar degeneration (PCD) is a subacute, and severe cerebellar syndrome, which is related to an underlying tumor. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a common cause of hyponatremia in patients with malignancies. We present a case of a 68-year-old Chinese female with concomitant LEMS, PCD and SIADH. Positron emission tomography revealed hypermetabolism in the upper lobe of the left lung, hilus of left side and lymph nodes in the hilum and mediastinum. Transbronchial lung biopsy confirmed small cell lung cancer. The clinical manifestations, as well as the biochemical, endocrinological, pathological, electrophysiological and imaging studies indicate that this is a very rare case with three PNSs associated small cell lung cancer. To our knowledge, this is the first report about a case of three PNSs in a small cell lung cancer patient. It is interesting and important to explore the underlying mechanisms in the future to help us understand the diseases, which indicate that multiple systems dysfunction are highly indicative of malignancy in the elderly.

Keywords: Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration, syndrome of inappropriate secretion of antidiuretic hormone

Introduction

Paraneoplastic syndromes (PNS) is not caused by direct invasion of tumor or its metastasis, but presumably immune mediated remote effects of cancer on other systems or organs [1]. Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disease of the neuromuscular junction, and approximately 50%-60% of patients with LEMS have a tumor, mostly small cell lung cancer (SCLC), which is usually detected after diagnosis of LEMS [2]. Paraneoplastic cerebellar degeneration (PCD) is most commonly associated with SCLC, cancer of the breast and ovary and lymphoma [3]. PCD was established by Brain and Wilkinson in 1965, and characterized by the subacute onset

of cerebellar dysfunction including gait difficulty and limb ataxia, sometimes associated with dysarthria, dysphagia, nystagmus, mental changes, muscular and sensory deficits [2]. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is frequently observed in the tumors with ectopic hormone production and is manifested by SIADH as a clinical symptom of hormone oversecretion. Usually the improvement of the symptoms can be seen after tumor excision. The classic tumor which represents 90% of these is oat cell carcinoma or undifferentiated carcinoma of the lung [4].

PCD sometimes occurs in association with LEMS, and this combination is not rare [2]. However, PCD and LEMS have never been

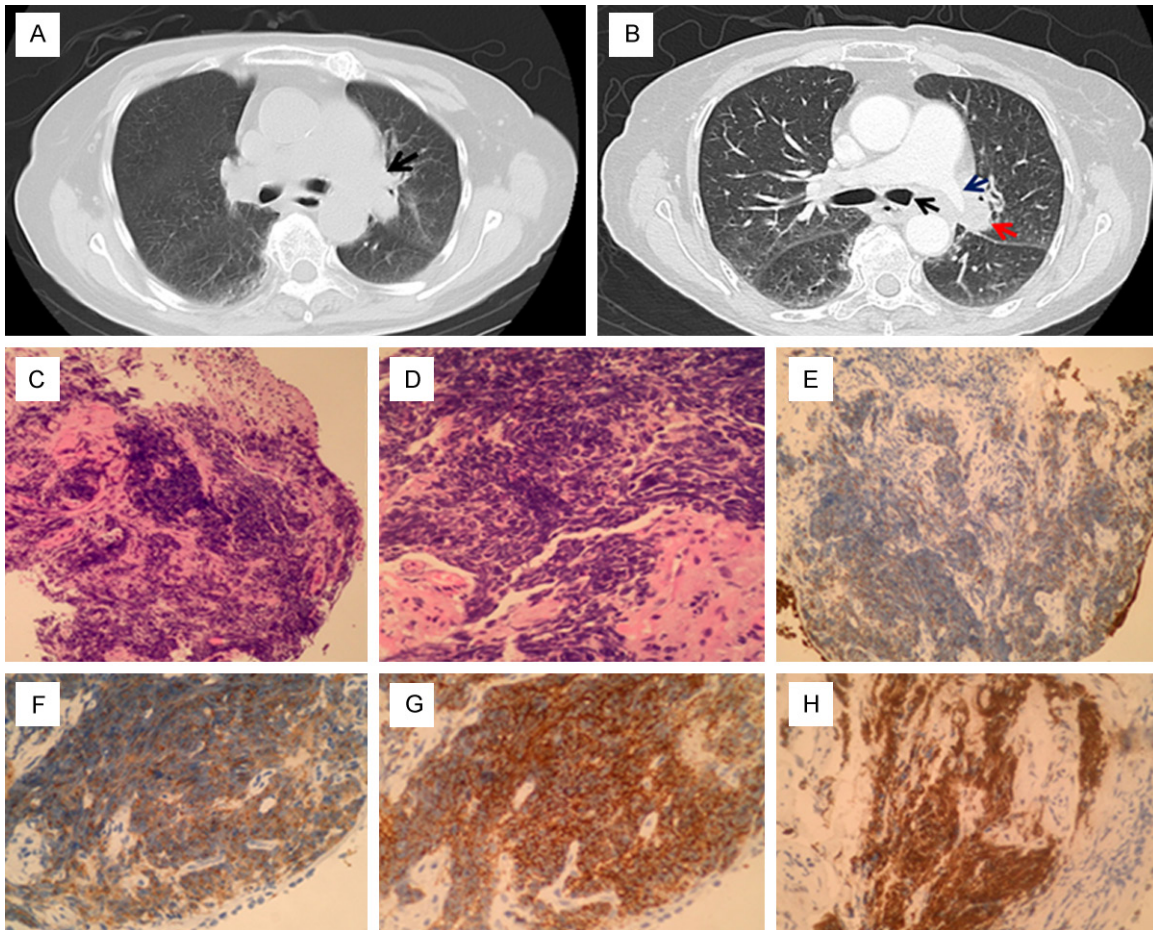


Figure 1. (A) Axial CT image of the hilum of pulmonary illustrates enlarged pulmonary hilum, diffuse interstitial fibrosis and left hilar lymphadenectasis, which was suspected of mass firstly. (B) Axial CT enhancement image of the hilum of pulmonary illustrates a mass with irregular shape and obvious enhancement in the apicoposterior segment of the superior lobe of left lung, which encompasses the left pulmonary artery and compresses the left pulmonary bronchi, the lesions had been suggested to be central lung cancer with left hilar lymph nodes metastasis. (C, D) Histology of small-cell carcinoma of lung in needle biopsy specimen. (C) A diffuse growth of small cells is noted in which small dark blue cells are packed together in sheets and (D) these small cells possess hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm (HE stain, original magnifications: C \times 100, D \times 400). (E-H) Immunostaining of small-cell carcinoma of lung in needle biopsy specimen. Cytokeratin (E), synaptophysin (F), CD56 (G) and TTF-1 (H) expression in tumor cells. Tumor cells expressed the cytokeratin and synaptophysin in cytoplasmic pattern. CD56 and TTF-1 immunostaining with positive membrane and nuclei respectively is indicative of tumor cells. (Immunostaining, original magnifications: E \times 200, F-H \times 400).

described in association with SIADH in one patient. Here we report a case with coexistence of LEMS, PCD and SIADH. To our knowledge, this kind of case has never been reported in medical literature.

Case report

A 68-year-old female was admitted to our hospital because of a 1-month history of speech and gait disturbance. She underwent a detailed medical history and did not have any specific chronic diseases. The initial neurological exam-

ination (NE) revealed only mild dysarthria and an unsteady gait. A brain MRI showed multiple subcortical lacunar infarcts bilaterally and a chest CT revealed diffuse interstitial fibrosis but no occupying lesions. The patient was diagnosed putatively with posterior circulation ischemia and was treated accordingly.

Over the following week the patient developed rapidly progressive cerebellar dysfunction with nystagmus, nausea, vomiting, limb ataxia, and titubation. Two weeks after admission the patient had difficulty swallowing and progres-

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sive limb weakness without diurnal fluctuation. A NE showed severe dysarthria, dysphasia, proximal muscle weakness, and absent deep tendon reflexes. A repeat brain MRI was the same as the initial scan, but chest CT revealed diffuse interstitial fibrosis and left hilar lymphadenectasis (**Figure 1A**). Meanwhile, a rapidly progressive hyponatremia was detected. The serum sodium level of 126.8 mmol/L was associated with a serum osmolality of 280 mosm/L, a urine osmolality of 382 mosm/L, and a urine sodium concentration of 43.2 mmol/L. Hypokalemia and hypochloremia were also observed simultaneously. TSH, free T4, T3, and a renal function panel were normal. Detailed electrophysiological studies were performed: a needle electromyography and nerve conduction study were unremarkable, but repetitive nerve stimulation (RNS) of the left common peroneal nerve showed a marked incremental response upon high-frequency stimulation (10 Hz and 20 Hz), whereas no significant decrement was observed on low-frequency stimulation (3 Hz). A contrast chest CT revealed a lobulated mass in the apicoposterior segment of the superior lobe of the left lung that encompassed the left pulmonary artery and compressed the left pulmonary bronchi (**Figure 1B**). SCLC was confirmed by a lung biopsy through a bronchoscope and subsequent pathological analysis (**Figure 1C-H**).

The patient was treated first with intravenous immunoglobulin and hypertonic saline with frequent monitoring of her serum sodium levels; the treatment was switched to isotonic saline infusion when her symptoms improved. She received chemotherapy with a regimen of etoposide and carboplatin for SCLC. Considering her multiple pulmonary metastatic lesions and poor condition, neither surgical procedures nor radiotherapy was pursued. Her status continued to deteriorate, and CT scan shows the occupying lesions increased in size during our follow-up.

Discussion

LEMS is a rare disorder with a well-characterized pathogenesis [5]. It appears to be caused by anti-presynaptic calcium channel antibodies [6]. LEMS is characterized by proximal muscle weakness that first affects gait, autonomic symptoms, augments strength during the initial voluntary activation, and depresses tendon

reflexes with post-tetanic potentiation [7]. The weakness, resulted from reduction in quantal release of acetylcholine from motor nerve terminals, is caused by autoantibodies against voltage-gated P/Q-type calcium channels (VGCCs) [7]. PCD is a sub-acute, severe cerebellar syndrome that is related to an underlying tumor. Although the pathogenesis of PCD is still not fully understood, the presence of antibodies against the antigens of Purkinje cells, the intrathecal synthesis of these antibodies and presence of inflammatory infiltrate in the cerebellum strongly suggest an autoimmune process [2]. Coexistence of LEMS and PCD are suggestive of an autoimmune etiology even though the mechanism underlying this phenomenon has largely remained elusive. Previous studies proposed that PCD occurs sometimes in association with LEMS [2]. However, it is possible that this association is not restricted to PCD, and those SCLC patients with paraneoplastic encephalomyelitis and sensory neuropathy also have an increased incidence of LEMS [2].

SIADH is a common cause of hyponatremia in patients with malignancies [8]. Hyponatremia is a common feature of malignancy-associated SIADH. SCLC is responsible for more than 60% of tumor-associated SIADH [9]. In Liamis's studies, electrolyte abnormalities are frequently observed in patients with hyponatremia, apart from hypophosphatemia, other electrolyte disorders have infrequently been described in patients with SIADH [10]. Taking into consideration the symptoms of nausea and vomiting, we conjecture that electrolyte disturbances in our patient should be ascribed mainly to the underlying cause of hyponatremia rather than to hyponatremia per se. Classic SIADH usually presents with hyponatremia; low serum osmolality; persistent urinary sodium excretion; euvoletic; normal renal function; and normal thyroid and adrenal function [11]. The diagnosis is often one of exclusion, with other causes of hyponatremia such as renal disease, liver and cardiac failure, psychogenic polydipsia and medications to be considered [12]. The possibility of excessive water ingestion, and medications, i.e, diuretics, induced alteration of serum sodium levels were carefully evaluated and excluded in our patient.

According to the diagnostic criteria for PNS described by the International Panel of

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Neurologists in 2004 [13], the present case could be diagnosed with definite PNS. The pathogenesis of multiple PNSs is not clear, although autoimmune mechanisms have been implicated. In conclusion, the current observations support the combination of LEMS, PCD, and SIADH in our case, which indicate that multiple systems dysfunction are highly indicative of malignancy in the elderly.

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Disclosure of conflict of interest

None.

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